I. Pending Claims and Priority Documents

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are being examined. Applicants submit for the Examiner's convenience APPENDIX "A" which includes a list of all the pending claims.

Applicants submit with this paper an English language, certified copy of priority document EP92-402644.6 (APPENDIX "B"), thereby perfecting applicants' claim of priority to that document. As discussed below, the claim to priority antedates references in each of the § 103 rejections. Applicants request acknowledgment of their claim to priority.

II. Rejection under 35 U.S.C. § 112, first paragraph

Claims 27-28, 31-34, 37-38, 40-41, and 48-50 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly does not enable the scope of these claims. Applicants respectfully disagree.

The Examiner reports that claims directed to cDNA encoding BDNF (brain-derived neurotrophic factor) and cDNA encoding prepro-BDNF (precursor protein) are enabled by the specification. That is why, apparently, claim 35 (reciting prepro-BDNF) is not rejected under 35 U.S.C. § 112, first paragraph. However, the Examiner contends that claims encompassing "any substance or derivative that may be named 'brain-derived neurotrophic factor'" are not enabled (*see* page 2 of the Office Action).

Applicants previously explained that one of ordinary skill in the art is familiar with, understands the meaning of, and has demonstrated an ability to use BDNF and prepro-BDNF. The various papers and patent documents that describe the protein have also been presented to

the Examiner (*see* pages 6 and 7, of Reply dated August 11, 1999 and EXHIBITS "A" through "D" thereto, specifically incorporated herein by reference). Since one skilled in the art understands what is meant by the abbreviation "BDNF," it is not clear why the Examiner persists in requiring some additional chemical or structural limitations for the claims to be considered enabled. Simply because the word "factor" is included in the name of the protein does not mean that it is a undefined mixture or extract, as in the "factors" referred to by endocrinologists in the 1970s. Many defined proteins are named using the word factor, *i.e.* CRF (corticotropin releasing factor) and GRF (growth hormone releasing factor). As in the case of BDNF, these are specific proteins and not an ill-defined extract.

Furthermore, Applicants submit that if some derivative of BDNF could be used in the vectors of the invention, one skilled in the art could easily test the ability of the vector encoding the derivative to function in a way described by the specification. Thus, one skilled in the art could make and use a BDNF derivative and test it for its biological activity. No requirement compels an applicant to specifically disclose every permutation or derivative of his invention before it can be considered enabling. *See* Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d. 1569, 1576-1577 (Fed. Cir. 1984).

In addition, the invention here, in an important aspect, provides a novel vector for delivering neurotrophic factors to appropriate cells. The invention is not, and enablement does not rest on, a particular neurotrophic factor. Therefore, Applicants are confused by the focus on structural and chemical limitations to BDNF.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Rejection of pending claims as obvious under Section 103(a)

In the Office Action mailed December 12, 2000, the Examiner rejected the pending claims based on Section 103(a) obviousness alleging unpatentability over (1) Barde *et al.* in view of Le Gal La Salle *et al.* and (2) Barde *et al.* in view of Wilson *et al.* Applicants respectfully traverse these rejections.

Applicants contend that the Barde *et al.* reference cannot establish obviousness on its own as it is directed solely to BDNF nucleic acid sequences, anti-BDNF antibodies, and the potential for BDNF protein therapy. The additional references, Le Gal La Salle *et al.* (February 12, 1993) and Wilson *et al* (June 7, 1993), are not available as prior art against the instant Application because they are antedated by Applicants' foreign priority document, European Patent Application No. EP92-402644.6 (September 25, 1992), the claim to which is now perfected by the enclosure of a certified, English language copy. Applicants detail the reasons that support the withdrawal of the obviousness rejections below.

(1) Rejection of Claims 27-28, 31-35, 37-38, 40-41, and 48-50 under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Le Gal La Salle *et al.*

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand rejected under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Le Gal La Salle *et al.* Applicants respectfully traverse this rejection. The combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Barde *et al.*

The Barde *et al.* document discusses nucleic acid sequences encoding porcine and human brain derived neurotrophic factor (BDNF) and the substantially pure BDNF protein, peptide fragments, or derivatives produced in quantity from these nucleic acid sequences (Figures 1 and 5). This reference also discusses antibodies directed toward the BDNF protein, peptide fragments, or derivatives. Barde *et al.* is concerned with producing sufficient quantities of BDNF to allow for anti-BDNF antibody production and to support diagnostic and therapeutic applications of BDNF protein (*see* column 10, lines 42-52 and columns 25-28).

Barde *et al.* fails to teach or suggest a replication defective recombinant adenovirus vector, particularly a vector with a non-functional E1 region. Specifically, Barde *et al.* fails to teach or suggest a replication defective recombinant adenovirus comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional. The reference certainly does not teach or suggest mammalian cells infected with such a replication defective adenovirus.

Le Gal La Salle *et al.*

The Le Gal La Salle *et al.* reference was published in Science in 1993. In previous replies mailed August 18, 1998 and August 11, 1999, Applicants set forth that the subject matter of the instant Application is entitled to priority under 35 U.S.C. §§ 119, 120, and 365 of co-pending U.S. Application Serial No. 08/403,868, filed April 28, 1995, which is the National Phase of PCT/EP93/02519, filed September 17,1993, which claims the benefit of European Patent Application No. EP92-402644.6, filed September 25, 1992. With Applicants' priority date

of September 25, 1992, the Le Gal La Salle *et al.* document is not available as "prior art" against the instant application.

In the Office Action mailed December 12, 2000, the Examiner asserted that the Applicants had failed to perfect the foreign filing date of September 25, 1992. In order to perfect their priority claim, Applicants hereby submit a certified, English language copy of European Patent Application No. EP92-402644.6, which was filed on September 25, 1992.

The Examiner also asserted that "Applicant's priority paper is not enabling for a replication defective recombinant adenovirus encoding BDNF because the disclosure is drawn to adenovirus encoding CNTF, HEXA, or NGF, but not BDNF." (*see* pages 5 and 6 of the Office Action). Applicants respectfully request that the Examiner reconsider this position in light of EP92-402644.6 (top of page 10), wherein the priority paper clearly discloses the expression "of the cDNA encoding . . . a growth factor such as BDNF (brain derived neurotrophic factor) . . .." The EP92-402644.6 document clearly shows the expression of a gene of interest in brain cells (*see, e.g.,* Assays 3 on pages 18 through 20) using an E1 deleted adenovirus (*see, e.g.,* page 5). EP92-402644.6 is therefore enabling, and Applicants are entitled to a priority date of September 25, 1992.

Given that the publication date of Le Gal La Salle *et al.* is February 12, 1993, this reference is not "prior art" to the instant application, and is therefore unavailable to make out a case for obviousness. As Barde *et al.* alone cannot render the claims obvious, Applicants respectfully request that this rejection be withdrawn.

(2) Rejecti n of Claims 27-28, 31-35, 37-38, 40-41, and 48-50 Under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Wilson *et al.*

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand rejected under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Wilson *et al.* (U.S. Patent No. 5,585,362). Applicants respectfully traverse this rejection. As detailed below, the Wilson *et al.* cited document is a result of many prior filings. None of the relevant filings contain the subject matter that the Examiner relies on in this rejection. Applicants' perfected claim to priority renders Wilson *et al.* unavailable as "prior art" here. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Barde *et al.*

As discussed above and in prior papers, the Barde *et al.* reference does not teach or suggest the claimed invention. In particular, Barde *et al.* does not suggest replication defective recombinant adenoviruses comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional. Barde *et al.* certainly does not suggest mammalian cells infected with such a replication defective adenovirus of the claimed invention.

Wilson *et al.*

The upcoming discussion of the Wilson *et al.* document involves several prior applications. Applicants' patent counsel will be available to clarify or otherwise discuss the Wilson *et al.* reference, or any other matter concerning this application, by telephone or personal interview at the Examiner's convenience.

The subject matter the Examiner has relied upon (*see* page 5 of Office Action) in Wilson *et al.* (U.S. Patent No. 5,585,362 issued December 17, 1996) has an effective U.S. filing date after Applicants' filing date. In previous replies mailed August 18, 1998 and August 11, 1999, Applicants set forth that the subject matter of the instant Application is entitled to priority under 35 U.S.C. §§ 119, 120, and 365 of co-pending U.S. Application Serial No. 08/403,868, filed April 28, 1995, which is the National Phase of PCT/EP93/02519, filed September 17, 1993, which claims the benefit of European Patent Application No. EP92-402644.6, filed September 25, 1992. With Applicants' priority date of September 1992, the Wilson *et al.* (effective filing date of June 7, 1993) document, is not available as "prior art" to the instant application.

As discussed above, the perfected priority paper EP92-402644.6 (September 25, 1992) is enabling for a replication defective recombinant adenovirus encoding BDNF, and Applicants perfect the September 25, 1992 priority date by submitting a certified, English language copy of EP02-402644.6.

On page 5 of the Office Action, the Examiner contends that the effective U.S. filing date of the Wilson *et al.* US 5,585,362 reference is September 11, 1992. Applicants respectfully disagree and submit that the Examiner has erroneously relied upon the disclosure of abandoned application Serial No. 07/943,952 (*see* "Related U.S. Application Data" section on page 1 of Wilson *et al.*) to obtain an effective filing date of September 11, 1992.[1] Application No. 073,354, which issued as Wilson *et al.*, is a continuation-in-part of 07/943,952. Application No. 07/943,952 discusses a xenograft model of an airway for the study of human cystic fibrosis; the application appears to neither claim nor disclose anything about BDNF, recombinant

[1] Serial No. 07/943,952 is attached as APPENDIX "C."

adenoviruses, cDNA, recombinant DNA, or gene therapy. Because Application No. 07/943,952 does not even mention adenovirus gene therapy, one cannot refer back to this application to establish an effective filing date for the Wilson *et al.* disclosure that the Examiner alleges teaches adenovirus gene therapy. Thus, the effective filing date of Wilson *et al.* cannot be September 11, 1992.

On page 6 of the Office Action, the examiner suggests that even if Serial No. 07/945,592 fails to establish an effective priority date, Wilson *et al.* can still claim priority to Serial Nos. 07/401,609 (August 31, 1989), 07/399,945 (August 24, 1989), and 07/396,894 (August 22, 1989).[2] Applicants respectfully disagree. None of the cited applications support an earlier effective filing date for Wilson *et al.* On page 5 of the Office Action, the Examiner lists the alleged advantages cited in the disclosure of Wilson *et al.* (when combined with Barde *et al.*) that allegedly render the instant Application obvious: the "many advantages for the adenovirus vector for gene therapy, including its approval for clinical trials, growth to extremely high titers for production purposes, usefulness in nondividing cells, and other reasons" (internal citations omitted). Serial Nos. 07/399,945 and 07/396,894 appear to be completely devoid of any reference to adenoviruses, much less the specific advantages alleged by the Examiner. While Serial No. 07/401,609 does use the term "adenovirus," the usage is simply to include the words "adenovirus" and "adeno-associated virus" in a lengthy listing of possible vectors. *See* Serial No. 07/401,609 at page 98, lines16-34, and page 107, lines 3-32, respectively; *see also* Serial No. 07/401,609 at page 100, lines11-12, page 113, lines 24-33, and page 116, lines 20-29

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[2] Copies of Serial Nos. 07/401,609, 07/399,945, and 07/396,894 are submitted herewith as APPENDICES "D" through "F" respectively.

("adenovirus" cited as a source for promoter derivation in long list of promoters). The use of the term "adenovirus" in no way teaches or suggests the specific Wilson *et al.* advantages alleged by the Examiner; thus, the 07/401,609 application cannot provide Wilson *et al.* with an earlier effective filing date because the disclosure cited by the Examiner in his obviousness rejection is absent from 07/401,609. Therefore Wilson *et al.* cannot claim priority back to Serial Nos. 07/401,609 (August 31, 1989), 07/399,945 (August 24, 1989), or 07/396,894 (August 22, 1989).

In addition to being a continuation-in-part of the previously discussed 07/945,592, Application No. 74,354 (June 7, 1993), which issued as Wilson *et al.*, is a continuation-in-part of Serial No. 067,296 (May 25, 1993), which is a division of Serial No. 584,275 (September 18, 1990), which is a continuation-in-part of the previously discussed 07/401,609, 07/399,945, and 07/396,894 applications. As Applicants show below, Wilson *et al.* cannot claim an effective U.S. filing date of September 18, 1990 based on Serial No. 584,275 for the subject matter the Examiner relies on in this rejection.

As mentioned in Applicants' reply mailed August 11, 1999, Serial No. 584,275, filed September 18, 1990, is now U.S. Patent No. 5,240,846.[3] The disclosure of 5,240,846 concerns gene therapy for cystic fibrosis through delivery and expression of a CFTR gene in the epithelial cells of a CF patient through the use of a retrovirus. Although alternative vectors (plasmids, liposomes, and DNA-protein complexes) are mentioned, use of adenoviruses is neither disclosed nor suggested. Applicants' disclosure (*e.g.*, EP92-402644.6, at pages 1-2) recounts the many disadvantages of utilizing retroviruses for gene therapy. The disclosure of Serial No. 584,274 is the same as the nonenabling disclosure of U.S. Patent No. 5,240,846, and therefore the filing

date of the 584,274 application (September 18, 1990) may not be used to establish an earlier priority for Wilson *et al.* Further, as a divisional application of Serial No. 583,275, the disclosure of the abandoned 067,296 application (May 25, 1993) must be considered the same as the nonenabling disclosure of U.S. Patent No. 5,240,846. Therefore, the subject matter of Wilson *et al.* cited by the Examiner must have been introduced after Applicants' priority date of September 25, 1992. For this reason, the Wilson *et al.* subject matter cited by the Examiner is not available as "prior art" against the instant application.

(b) Barde *et al.* does not render obvious the invention of claims

As discussed above, Barde *et al.* does not teach or suggest the claimed invention. Barde *et al.* fails to teach or suggest a replication defective recombinant adenovirus vector. Specifically, Barde *et al.* fails to teach or suggest a replication defective recombinant adenovirus comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional. This reference certainly does not teach mammalian cells infected with such a replication defective adenovirus. Barde *et al.* cannot possibly render *prima facie* obvious the invention defined by Applicants' independent claims 27, 35, and 37, or the claims dependent thereon.

[3] U.S. Patent No. 5,240,846 was previously provided to the Examiner as EXHIBIT "F" in the August 11, 1999 Reply.

Contingency for Unexpected Fees

No further extension of time fees, requests for extension of time, petitions or additional claim fees are believed to be necessary to enter and consider this paper or keep this application pending. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims or any petitions needed to keep this application pending, applicants hereby request the extensions and/or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account # 50-1129 for any fees.

Respectfully submitted,
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Date: August 14, 2001

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APPENDIX A

U.S. Patent Application Serial No. 08/716,209
"Recombinant Adenoviruses Coding for Brain-Derived Neurotrophic Factor (BNDF)"
WRF File No. ST94014-US
Claims Being Examined

27. A replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophic factor (BDNF), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system.

28. The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA encodes prepro-BDNF.

31. The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA encodes human prepro-BDNF.

32. The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA is operably linked to a signal controlling expression in a nerve cell.

33. The replication defective recombinant adenovirus according to Claim 32, wherein the signal is a viral promoter.

34. The replication defective recombinant adenovirus according to Claim 33, wherein the signal is selected from the group consisting of an RSV-LTR promoter, an E1A promoter, an MLP promoter, and a CMV promoter.

35. A replication defective recombinant adenovirus comprising a cDNA encoding human prepro-BDNF, operably linked to an RSV-LTR promoter, wherein the adenovirus E1 gene is non-functional.

37. A replication defective recombinant adenovirus comprising a cDNA encoding human brain-derived neurotrophic factor (hBDNF) operably linked to a promoter controlling expression in a nerve cell, wherein the adenovirus E1 gene is non-functional.

38. The replication defective recombinant adenovirus according to Claim 37, wherein the promoter is selected from the group consisting of a neuron-specific enolase promoter and a GFAP promoter.

40. The replication defective recombinant adenovirus according to Claim 27, comprising ITRs and a sequence permitting encapsulation, wherein the E1 gene and at least one of the E2, E4 or L1-L5 genes are nonfunctional.

41. The replication defective recombinant adenovirus according to Claim 27, wherein the replication defective recombinant adenovirus is a type Ad 2 or Ad 5 human adenovirus or a CAV-2 type canine adenovirus.

48. A mammalian cell infected with the replication defective recombinant adenovirus according to Claim 27.

49. The mammalian cell according to Claim 48, wherein the mammalian cell is a human cell.

50. The mammalian cell according to Claim 49, wherein the mammalian cell is selected from the group consisting of a fibroblast, a myoblast, a hepatocyte, an endothelial cell, a glial cell, and a keratinocyte.